REMARKS

Claims 1, 3, 5, 6, 14, and 15 are pending in the application.

Claims 2, 4, 7-13, 16-67 have been previously cancelled without prejudice.

Claims 1, 3, and 5 are amended to obviate rejections under 35 U.S.C. 112, second paragraph. No new matter is added by these amendments.

Claims 1, 3, 5, 6, 14, and 15 are not obvious over Freed *et al.* alone or the combination of Freed *et al.* and Przybyszewska *et al.*

The rejection under 35 U.S.C. §103(a) of claims 1, 3, 5, 6, 14 and 15 as allegedly being obvious over Freed *et al.* alone or the combination of Freed *et al.* and Przybyszewska *et al.* is traversed because *prima facie* obviousness has not been established. In order to establish a *prima facie* case for obviousness, all claim limitations must be taught or suggested by the prior art. *In re Royka*, 180 USPQ 580 (CCPA 1974). That is not the case here. Also, "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 165 USPQ 494, 496 (CCPA 1970), and "Difference between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter," *In re Gulack*, 217 USPQ 401, 403 (Fed. Cir. 1983).

Freed *et al.* is directed to complexes of Raf-1 (c-Raf) and human 14-3-3 proteins, as well as to methods for identifying novel drugs that modulate Raf-1 activity *in vivo* (see Abstract and claims). Freed *et al.* discloses the structure of Raf-1 protein and various fragments thereof. Freed *et al.* also describes interactions between these proteins and human 14-3-3 proteins.

The present claims, on the other hand, are directed to articles of manufacture, not to pharmaceutical compositions. The present claims also are not directed to specific Raf compounds *per se* or to methods. The presently claimed articles of manufacture must include the following components:

1. packaging material;

2. a pharmaceutical composition capable of stimulating angiogenesis within the packaging material, which includes at least 0.1 weight percent of a compound selected from:

(a) c-Raf,

(b) residues 306-648 of c-Raf, and

(c) Raf-caax,

in a physiologically acceptable excipient or carrier; and

3. a label containing specified printed matter setting forth instructions and directions for certain uses of the composition.

Freed *et al.* do not teach or suggest all of these limitations. In particular they do not teach or suggest a composition having at least 0.1 % by weight of the specific active Raf proteins contained within packaging material that has a label affixed thereto bearing certain information. The Examiner's own unsupported testimony as to what is "customary" for concentrations is of no moment, and does not support the present rejection. Nor do Freed *et al.* teach or suggest that the Raf proteins stimulate angiogenesis, which is the subject matter of the writing on the label. Accordingly, this reference, alone, cannot possibly render claim 1 obvious. Freed *et al.* does not teach or suggest all of the limitations of the claim.

Przybyszewska *et al.* is directed to angiogenesis induced by urothelial cells that have been transformed by v-Ras and v-Raf, not to c-Raf or fragments of c-Raf. This reference does not teach or suggest that c-Raf or its fragments, as isolated materials, can stimulate angiogenesis. Neither this reference nor Freed *et al.* suggest the combination attempted by the Examiner. There exists no basis whatsoever to equate cells transformed by v-Raf to c-Raf complexes. Moreover, even the attempted combination does not teach or suggest that c-Raf or its fragments have utility in a pharmaceutical composition or in an article of manufacture containing such a composition.

It must also be noted that Przybyszewska *et al.* is directed to v-Raf and v-Ras transfected cells not to Raf-1 (c-Raf)-containing compositions as is Freed *et al.* One of ordinary skill in the art would not have been motivated to combine the teachings of these two references, inasmuch as these references deal with different compounds and different concepts (v-Raf transformed cells versus Raf-1/14-3-3 protein complexes). Moreover, even the combined references do not teach or suggest the packaging material, the minimum level of 0.1% Raf protein, or the label with its included written matter. Accordingly, the present claims are clearly

patentable over this combination of references.

Claims 1, 3, 5, 6, 14, and 15 are not obvious over Kolch *et al.* or the combination of Kolch *et al.* and Przybyszewska *et al.*

Claims 1, 3, 5, 6, 14, and 15 stand rejected under 35 U.S.C. §103(a) as allegedly being obvious over Kolch *et al.* or the combination of Kolch *et al.* and Przybyszewska *et al.* This rejection is traversed as well.

Kolch *et al.* describe preparation of human c-Raf expression vectors and transfection of cells with those vectors. This reference, however, does not teach or suggest that c-Raf, *per se*, has utility in a pharmaceutical composition, nor does this reference teach or suggest an article of manufacture containing a minimum of 0.1% of c-Raf or its fragments in packaging material having a label including specific written matter affixed thereto. All of the limitations of the present claims are neither shown nor suggested. The record here lacks any evidentiary showing that a c-Raf concentration of at least 0.1% is "customary."

The teachings of Przybyszewska *et al.* were discussed above and are equally applicable here. The attempted combination of Kolch *et al.* and Przybyszewska *et al.* is not warranted because no valid basis for the attempted combination can be found in either reference. Even if, arguendo, this combination is deemed to be proper, it fails to teach or suggest all of the limitations of the claims. At best, the combination of these two references might have motivated one of ordinary skill in the art to transfect a urothelial cell line with c-Raf to test whether c-Raf transfected cells behave like the v-Raf transfected cells of Przybyszewska *et al.* This is nothing but an invitation to experiment. Such a combination would not have motivated one of ordinary skill in the art to construct the articles of manufacture specified by the present claims. This combination of references fails to suggest any article of manufacture, much less one defined by the present claims.

Label Does Indeed Impart Specific Functionality to the Claimed Article

The Examiner contends that printed words on a label cannot be given patentable weight unless the article is changed by the written matter. Applicants respectfully submit that this is precisely the case with the present claims. The label is an integral part of the claimed article. In the present case, one of ordinary skill in the art would not have been able to use the

claimed articles of manufacture to stimulate angiogenesis, since this concept was unknown to one of ordinary skill in the art at the time the invention was made. In claim 1, the printed matter on the label must be given patentable weight because the instructions and information on the label do indeed impart specific functionality to the article of manufacture that was previously unknown to one of ordinary skill in the art. The printed matter further distinguishes the claimed articles of manufacture from other articles of manufacture. Furthermore, the information on the label *vis-a-vis* the ability of Raf proteins to stimulate angiogenesis is novel, and informs the user of the article how the claimed article is to be utilized. This label limitation is analogous to the situation in *Miller* where the item at issue was a measuring cup. Without the printed matter, the cup had a utility of its own. With the printed matter, the measuring cup had a new and distinct utility (facilitating the preparation of fractional portions of a recipe without the need for mathematical calculations). The printed matter was specifically claimed to be "on" the cup. This sufficed to provide the structural relationship necessary to carry out the invention. See *In re Miller*, 164 USPQ 46, 49 (CCPA 1969):

> "... printed matter, in an article of manufacture claims, can be given patentable weight ... no attempt is here being made to patent printed matter as such. The fact that printed matter by itself is not patentable subject matter, because non-statutory, is no reason for ignoring it when the claim is directed to a combination ... The solicitor seems to urge that we ignore the claim limitations to the legends because they are printed and because printed matter is not patentable subject matter by itself ... we reject that argument."

Applicants take exception to the Examiner's comments that *Miller* and *In re Gulack* are not applicable here. In *Miller*, prior to adding the printed matter onto the measuring cup, that cup had utility as a simple cup. The new printed matter on the cup did not alter the structure of the cup but conveyed a new utility not previously known to one of ordinary skill in the art. Similarly, *In re Gulack*, 217 USPQ 401, 403 (Fed. Cir. 1983) involved a band imprinted with a series of digits derived from a mathematical algorithm. The band could be a hat band, for example, having utility on its own. Before the application of the printed matter, the band could be used as a hat band, or for other purposes. Adding the new printed matter onto the band conveyed a new utility that was not previously known to one of ordinary skill in the art, i.e., it

was now useful for performing "magic tricks" and for displaying various aspects of number theory. The Court found that the band supported the numbers and the numbers had a relationship to each other that provided a new utility to the band.

Clearly, in the present claims, the printed matter conveys a new utility to an article of manufacture that was not known in the prior art. Furthermore, while the compounds per se may have been known, their inclusion in the packaged composition and in the specified amounts together with a label, as an article of manufacture, was not known, and is not taught or suggested by Freed *et al.* alone or in combination with the secondary reference. Accordingly, the present claims are clearly patentable over the applied references.

In re Ngai, 70 USPQ 1862 (Fed. Cir. 2001) is readily distinguishable. The prior art in that case already taught a kit and the necessary 10X buffer therefor. That is not the situation here. The specific composition defined by the claims is not in the prior art, neither is a packaged version of that composition as claimed. The new printed matter unquestionably conveys new utility, a new feature, to the package, not previously known to one of ordinary skill in the art.

Conclusion

Claims 1, 3, 5, 6, 14, and 15 as currently amended meet all of the requirements of 35 U.S.C. §112 and are patentable over the applied art. Reconsideration of the rejections and early passing of this application to issue is earnestly solicited. In the event the Examiner deems the foregoing analysis and discussion not persuasive, entry of the current amendments is requested in order to place this application in better condition for appeal.

Respectfully submitted,

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